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Review

Influence of different exercise types on vascular endothelial function in middle-aged and older adults – A systematic review and network meta-analysis

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HIGHLIGHTS

- This is the first network meta-analysis on FMD in middle-aged and older adults.
- Aerobic exercise is the best way to improve FMD in middle-aged and older adults.
- Using SUCRA, this study assesses the efficacy of various exercise interventions.
- The results offer evidence for tailored exercise prescriptions for older adults.
- Results offer valuable evidence for clinicians to create tailored exercise prescriptions.

ARTICLE INFO

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ABSTRACT

Study Objectives: Against the current backdrop of population ageing, the correlation between cardiovascular diseases and endothelial dysfunction is increasingly important. Exercise, a simple and accessible method of preventing and ameliorating numerous diseases, has been demonstrated to significantly enhance endothelial function. This study aimed to assess the effects of aerobic exercise (AE), resistance exercise (RE), combined exercise (CE) and high-intensity interval training (HIIT) on vascular endothelial function in middle-aged and older adults. Flow-mediated dilation (FMD) is a non-invasive ultrasound technique used to measure endothelial function. Direct and indirect comparisons were used to determine which exercise modality most effectively improved vascular endothelial function in this demographic.

Methods: This comprehensive systematic review and network meta-analysis examined randomised controlled trials (RCTs) comparing the effects of four different exercise interventions (AE, RE, CE and HIIT) to a control intervention on FMD in middle-aged and older adults.

Results: The analysis included 20 RCTs involving 1,123 participants. The surface under the cumulative ranking curve (SUCRA) analysis indicated that AE was the most effective in improving FMD (SUCRA = 68.9 %), followed by HIIT (SUCRA = 62.5 %), RE (SUCRA = 58.8 %), CE (SUCRA = 54.9 %) and CON (SUCRA = 4.9 %).

Conclusions: This network meta-analysis of various interventions for FMD in middle-aged and older adults found that AE was the most effective in improving FMD (SUCRA = 68.9 %). These findings suggest that AE could be a valuable intervention in clinical practice for enhancing vascular health in this population.

1. Introduction

Population ageing has become a pressing issue globally. According to a 2022 report by the World Health Organization, those aged ≥65 years are projected to increase to 1.6 billion by 2050, constituting 16 % of the global population (Lin et al., 2020). The challenges accompanying this demographic shift are predominantly health-related and include elevated prevalences of conditions such as cardiovascular diseases,

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hypertension, diabetes and cancer, all of which entail significant treatment costs. In China, the prevalence of diabetes in adults increased from 9.7 % in 2007 to 11.2 % in 2017 (Li et al., 2020). Furthermore, the prevalence of hypertension has increased substantially over the past three decades, now affecting approximately one-quarter of adults (Wang et al., 2023). Chronic ailments such as hypertension and diabetes are intricately linked to cardiovascular disease risk factors and endothelial dysfunction (De Vriese et al., 2000; Taddei et al., 1996).

Endothelial cells form a delicate, single layer of flattened cells that line the inner surfaces of the heart, blood vessels and lymphatic vessels (Trimm and Red-Horse, 2023). Their pivotal roles include facilitating the transport of oxygen and nutrients, regulating blood flow dynamics, assisting in immune cell trafficking and preserving tissue equilibrium. Moreover, they orchestrate the intricate balance of vascular tone by synthesising and releasing a spectrum of endothelium-derived mediators, including nitric oxide (NO) and vasoconstrictors (Godo and Shimokawa, 2017).

Endothelial dysfunction is primarily caused by reduced production of vasodilators or impaired endothelial cell function. This dysfunction is increasingly recognised as a critical precursor to cardiovascular diseases, prompting greater scrutiny. Various methods exist to assess endothelial function, with measuring the flow-mediated dilation (FMD) of the brachial artery emerging as the most widely used (Creager et al., 2012). Previous studies have underscored the independent prognostic capability of FMD to predict cardiovascular events (Inaba et al., 2010; Green et al., 2011). For individuals without pre-existing cardiovascular conditions, each 1 % increase in FMD corresponds to a 4 % decrease in cardiovascular risk (Ras et al., 2013). Conversely, for those with cardiovascular risk factors such as hypertension, every 1 % increase in FMD correlates with a 13 % reduction in cardiovascular risk (Inaba et al., 2010). Therefore, preventing and reducing endothelial dysfunction is crucial.

As a simple and accessible method, exercise not only lowers the risk of cardiovascular diseases but also enhances endothelial function. A meta-analysis confirmed that exercise training, particularly aerobic (AE) and combined (CE) exercise, improved endothelial function in individuals with type 2 diabetes (Qiu et al., 2018). Another meta-analysis similarly suggested that concurrent training can enhance endothelial function and reduce arterial stiffness in those with type 2 diabetes (Chen et al., 2023). Similarly, another review reported that exercise training could improve endothelial function in healthy postmenopausal women (Lew et al., 2022).

Notably, exercise training has been shown to improve endothelial function in individuals with hypertension. A systematic review on endothelial function in individuals with prehypertension and hypertension indicated that regular moderate-intensity AE could effectively enhance vascular health in individuals with hypertension, high-intensity interval training (HIIT) could benefit vascular health in individuals with prehypertension and resistance exercise (RE) would serve as an adjunctive option for improving endothelial function (Waclawovsky et al., 2021). Additionally, AE was found to be beneficial for endothelial function in individuals who are overweight and obese (Cortes et al., 2023). Moreover, both AE and RE positively impacted endothelial function in healthy adults (Shivgulam et al., 2023). Furthermore, exercise training even improved endothelial function in patients with heart failure with reduced ejection fraction (Pearson and Smart, 2017).

However, the results of studies on the effects of different exercise modalities on endothelial function in middle-aged and older adults are inconsistent. Various exercise modalities, such as AE, RE and HIIT, may affect FMD differently in this demographic. Which exercise modality most effectively improves endothelial function in middle-aged and older adults is currently unclear.

Therefore, this systematic review and network meta-analysis aimed to evaluate the specific effects of various exercise modalities on vascular endothelial function, as assessed by FMD, in middle-aged and older adults to provide scientific evidence for promoting vascular health in this demographic. This comprehensive evaluation of existing studies aimed to reveal the extent to which different exercise modalities affect vascular endothelial function in middle-aged and older adults and identify the most effective exercise interventions. We hypothesised that AE more effectively improves endothelial function in middle-aged and older adults than other exercise modalities.

2. Materials and methods

The study was developed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The extended PRISMA statement for network meta-analyses ensures accurate reporting of the study's methods and results (Welch et al., 2015). The study protocol was registered in the PROSPERO database (registration number: CRD42024542666).

2.1. Search strategy

The following electronic databases were searched: PubMed, Excerpta Medica Database (EMBASE), Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP) and Wanfang (English and Chinese). The selection criteria and operationalised methods were based on the Population, Intervention, Comparison, Outcome, and Study design (PICOS) principles. The specific search terms used in the search strategy included various medical and free-text terms related to middle-aged and older adults, endothelium and exercise to obtain a comprehensive set of studies for further analysis. A broad and reproducible search of the seven databases using the above methodology was conducted in April 2024. Table 1 presents the search strategy used for the PubMed database as an example of the study's search methods.

2.1.1. Inclusion criteria

Based on the PICOS framework, the inclusion criteria were as follows: (1) The population was middle-aged and older adults aged 45–85 years (Dogra et al., 2018) who were either healthy or had non-life-threatening chronic diseases such as hypertension, type 2 diabetes, and metabolic syndrome; (2) the intervention was one of four exercise modalities (AE, CE, RE and HIIT); (3) the comparison was to a control (CON) group that received health education, including nutrition advice, lifestyle guidance and psychological support, or maintained their original lifestyle; (4) the primary outcome was FMD; (5) the adopted study design was a randomised controlled trial (RCT) to ensure balanced baseline characteristics between the intervention and CON groups.

2.1.2. Exclusion criteria

Studies meeting any of the following criteria were excluded from the analysis: (1) focused on individuals with major mental illnesses, such as major depression, bipolar affective disorder or schizophrenia, or those

Table 1
PubMed search strategies.

	Search Strategy
#1	(endothelium OR Endotheliums)
#2	(aged OR senior citizen OR Middle Age OR Middle Aged OR Middle-aged and elderly)
#3	(Exercises OR Physical Activity OR Activities, Physical OR Activity, Physical OR Physical Activities OR Exercise, Physical OR Exercises, Physical OR Physical Exercise OR Physical Exercises OR Acute Exercise OR Acute Exercises OR Exercise, Acute OR Exercises, Acute OR Exercise, Isometric OR Exercises, Isometric OR Isometric Exercises OR Isometric Exercise OR Exercise, Aerobic OR Aerobic Exercise OR Aerobic Exercises OR Exercises, Aerobic OR Exercise Training OR Exercise Trainings OR Training, Exercise OR Trainings, Exercise OR Exercise)
#4	(randomized controlled trial OR randomized OR placebo)
#5	#1 AND #2 AND #3 AND #4

without life-threatening diseases; (2) involved animals rather than humans or cell experiments; (3) did not clearly specify participants' age range or health status or did not classify them as middle-aged or older adults; (4) did not use brachial artery FMD as a primary outcome measure; (5) lacked detailed method descriptions, making it difficult to clearly articulate the data collection and analysis process; (6) there was a noticeable baseline imbalance or randomisation issue between the intervention and CON groups; (7) the study was a systematic review, meta-analysis, theoretical analysis, expert review, conference paper, economic analysis or case report.

2.2. Article screening

The retrieved articles were screened and analysed using the EndNote Reference Manager software (version X20; Clarivate, Philadelphia, PA, USA). The selection process included the following steps: (1) Preliminary screening, in which three reviewers (QC, XG and CW) initially screened article titles and abstracts against the predefined inclusion and exclusion criteria, considering factors such as study population, intervention measures and primary study design; (2) full-text assessment of the articles that passed Step 1, focusing on a detailed examination of their methods, sample sizes, primary outcome measures and other relevant details; (3) discussions until a consensus is reached on any disagreements on the inclusion of articles among the three reviewers, during which they carefully examined each article's contributions and methodological quality to ensure fairness and accuracy in the final evaluation; (4) expert consultation with a fourth researcher (PZZ) for articles for which a consensus could not be reached among the three reviewers, ultimately determining their inclusion or exclusion.

2.3. Data extraction and quality assessment

Data was extracted using Microsoft Excel (version 2019; Santa Rosa, CA, USA). XG, QC, and CW were primarily responsible for data screening and extraction. XG and QC extracted and organised pertinent information into tables, including study titles, authors, publication years, intervention types and frequencies, primary outcome measures, and exercise intensities. They conducted quality checks on the included articles. In cases of disagreement during data extraction, XG and QC consulted CW, and all discrepancies were resolved through joint discussion.

The included RCTs were assessed for potential risk of bias using the Cochrane Risk of Bias tool (Julian and James, 2023), which includes an evaluation of appropriate sequence generation methods, allocation concealment, blinding of participants and staff, incomplete outcome data, selective reporting and other sources of bias (e.g. early trial termination and extreme imbalance at baseline). The RCTs were categorised based on their methodological quality as having a low, high or unclear risk of bias. Two reviewers (QC and XG) independently assessed the studies' risk of bias, and a third reviewer (CW) resolved any disagreements through joint discussion.

2.4. Statistical analysis

A network meta-analysis of continuous variables was conducted using Stata software (version 16; StataCorp LLC, College Station, TX, USA). The analysis was performed using the 'network' extension, which allows for the application of a consistency effects model to merge effect sizes across different studies. The consistency model attempts to adjust and explain heterogeneity among studies (i.e. the differences between studies) to ensure consistency and comparability when comparing intervention measures. More accurate estimates of the relative effects of different interventions can be obtained through the consistency model, further assessing their relative efficacy on specific outcomes.

The 'network' command was used to generate network plots and forest plots, which visually display the comparative results and estimates of effect sizes between various interventions. As all included RCTs used the same outcome measure, the mean difference (MD) and its corresponding 95 % confidence interval (CI) were calculated. All directly or indirectly comparable data were visualised as a forest plot, and each intervention was ranked based on the surface under the cumulative ranking curve (SUCRA), resulting in a relative ranking for each intervention (Salanti et al., 2011). SUCRA is a method used in meta-analysis to compare the effects of multiple interventions. It evaluates the relative positions of each intervention across all possible rankings, generating a percentage value. A higher SUCRA value, closer to 100 %, indicates that the exercise modality ranks best across all comparisons, performing optimally regarding exercise effectiveness. Conversely, a lower SUCRA value, closer to 0 %, indicates a worse ranking of the exercise modality across comparisons.

All statistical analyses were performed using the Stata/MP software (Chaimani & Salanti, 2015). In addition, funnel plots were generated to show article publication bias. In a network evidence graph, each node represents an exercise intervention, and its size corresponds to the sample size of the intervention groups. A straight line connecting two nodes indicates a direct comparison, and the absence of a straight line indicates an indirect comparison. The thickness of the line connecting two nodes represents the size of the initial test sample. Both the nodes' size and the lines' thickness are proportional to the number (White et al., 2012). We will assess the risk of bias for each RCT using RevMan software (version 5.3; The Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Study identification and selection

The search of the seven databases using the specified search terms identified 2735 articles, and an additional 134 original studies were identified through manual searching (searched the reference lists of the identified articles). After eliminating duplicates, 1966 unique articles remained, and their titles and abstracts were screened against the inclusion and exclusion criteria. The full texts of 622 articles were then read, of which 184 were excluded due to their study purpose, 75 due to their intervention, 113 due to their outcome indicators, 86 due to their study type (non-RCT) and 124 due to their data format. Therefore, 20 studies were included in the risk assessment and network meta-analysis. The article screening process is shown in Fig. 1.

3.1.1. Included RCTs' characteristics

The 20 RCTs included 628 participants in the intervention groups and 495 in the CON groups. The shortest intervention duration was eight weeks, and the longest was one year. The intervention groups participated in one of the four intervention types: AE, CE, RE and HIIT. The included articles were published from 2007 to 2023. Table 2 details the basic characteristics of the included RCTs.

Twenty studies were included in the analysis (Mitranun et al., 2014; Gholami et al., 2020; Okada et al., 2010; Kwon et al., 2011; Liu et al., 2007; Azadpour et al., 2017; Fecchio et al., 2023; Lv et al., 2019; Barone Gibbs et al., 2012; Luo, 2021; Sun, 2019; Lu et al., 2012; Bouaziz et al., 2019; Haynes et al., 2021; Hildreth et al., 2018; Mai, 2022; Wu, 2021; Chen et al., 2022; Wang, 2019; McDermott et al., 2009), 8 in Chinese and 12 in English. Among them, 5 studies included subjects with only diabetes and prediabetes (Mitranun et al., 2014; Gholami et al., 2020; Okada et al., 2010; Kwon et al., 2011; Liu et al., 2007), 3 studies included subjects with only hypertension and prehypertension (Azadpour et al., 2017; Fecchio et al., 2023; Lv et al., 2019), 2 studies included subjects with both diabetes and hypertension (Barone Gibbs et al., 2012; Luo, 2021), 2 studies included subjects with metabolic syndrome (Sun, 2019; Lu et al., 2012), 8 studies included subjects without apparent metabolic disorders (Bouaziz et al., 2019; Haynes et al., 2021; Hildreth et al., 2018; Mai, 2022; Wu, 2021; Chen et al., 2022; Wang, 2019; McDermott et al., 2009) and 11 studies included

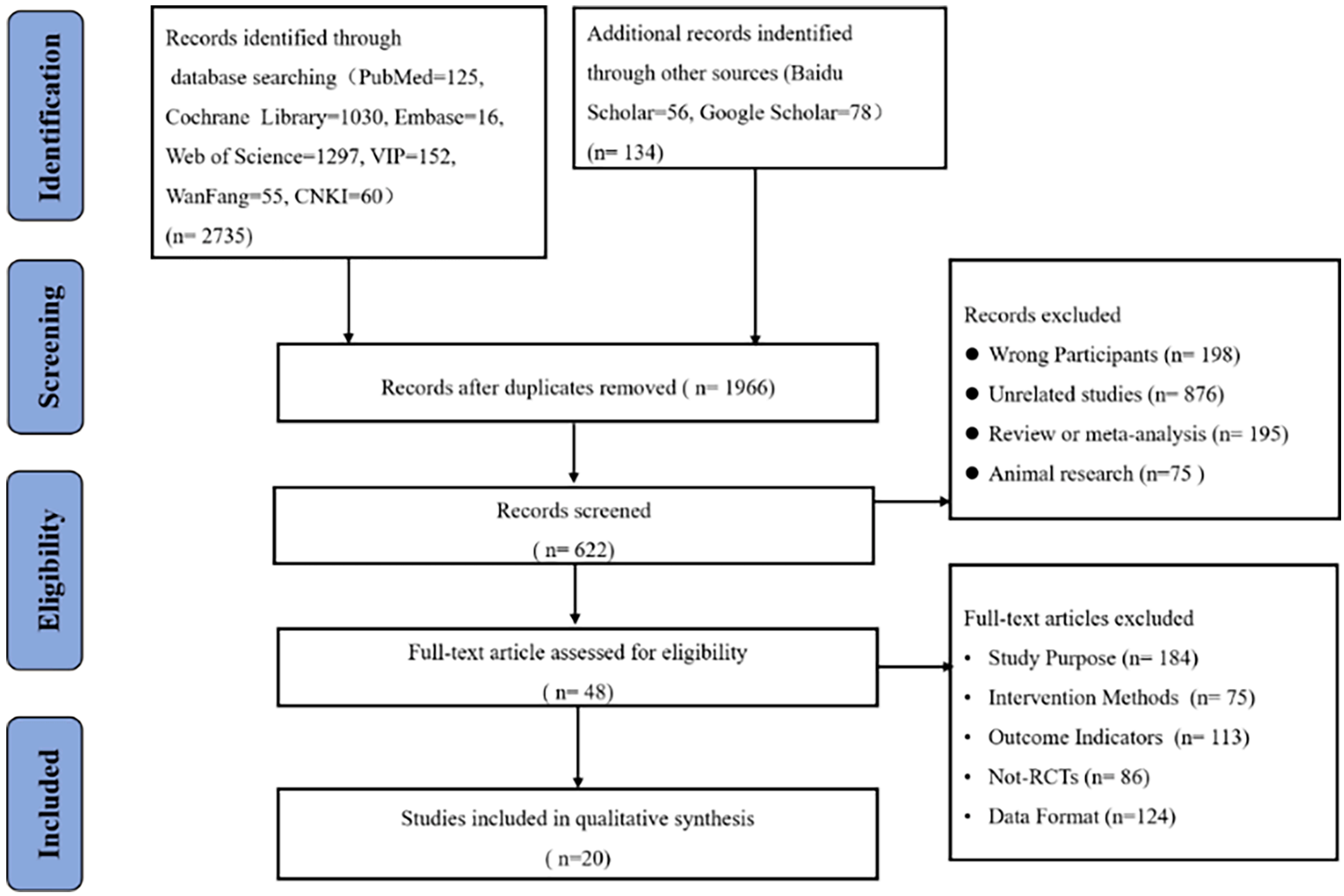

Fig. 1. PRISMA flowchart of the selection process of eligible studies.
n = number of publications.

subjects who were either overweight or obese (Mitranun et al., 2014; Gholami et al., 2020; Okada et al., 2010; Kwon et al., 2011; Azadpour et al., 2017; Fecchio et al., 2023; Barone Gibbs et al., 2012; Lu et al., 2012; Bouaziz et al., 2019; Hildreth et al., 2018; Wang, 2019).

3.1.2. Quality assessment of the included RCTs

Each RCT's risk of bias was assessed using the RevMan software. Regarding random sequence generation, 25 % of the RCTs had low risk, 70 % had unclear risk and 5 % had high risk. Regarding allocation concealment, 20 % of the RCTs had low risk, 55 % had unclear risk and 25 % had high risk. Regarding blinding of participants and personnel, 35 % of the RCTs had low risk, 35 % had unclear risk and 30 % had high risk. Regarding blinding of outcome assessments, 55 % of the RCTs had low risk, 30 % had unclear risk and 15 % had high risk. Regarding incomplete outcome data, 80 % of the RCTs had low risk, 5 % had unclear risk and 15 % had high risk. Regarding selective reporting, 40 % of the RCTs had low risk, 50 % had unclear risk and 10 % had high risk. Regarding other biases, 40 % of the RCTs had low risk, 50 % had unclear risk and 10 % had high risk. Detailed information in Fig. 2.

3.2. Outcome

The direct and indirect comparisons identified in the network diagram revealed closed loops forming within the sequences AE, CE and CON; AE, RE and CON; and AE, HIIT and CON. Furthermore, the inconsistency assessment yielded a *P*-value >0.05, indicating high consistency and reliability of the research findings. The inconsistency testing conducted on the closed-loop systems failed to reveal any significant inconsistencies, highlighting the study's robust consistency and stability.

3.2.1. Network meta-analysis results

This network meta-analysis included 20 RCTs with 1123 participants comparing four interventions (AE, CE, RE and HIIT) to the CON. All 20 RCTs were included in the network evidence map for the primary outcome of FMD. Fig. 3 presents the network meta-analysis diagrams.

3.2.2. FMD

The network meta-analysis included 20 RCTs evaluating FMD. It revealed that in the direct comparisons, both AE (MD = 1.54, 95 % CI = 0.75–2.34) and RE (MD = 1.34, 95 % CI = 0.37–2.31) differed significantly from the CON, with two SUCRA value of 68.9 % and 58.8 %, indicating their superiority over the CON. The indirect comparisons (Table 3) revealed no significant differences among the intervention types.

A SUCRA value closer to 1 indicates that the intervention ranks higher across various outcome measures, indicating better performance. The SUCRA value does not refer to the entire area under the SUCRA curve but rather the cumulative area under the SUCRA curves for each intervention. A larger area indicates that the intervention's performance is more stable and consistent across all evaluated outcomes (Fig. 4). The calculated SUCRA values indicated that AE ranked first in improving FMD (SUCRA = 68.9 %), followed by HIIT (SUCRA = 62.5 %), RE (SUCRA = 58.8 %), CE (SUCRA = 54.9 %) and CON (SUCRA = 4.9 %). The relative treatment rankings are detailed in Table 4.

Table 2
The basic characteristics of the included RCTs.

Author	Location	Duration of intervention	Frequency	Time	Group	N	Sex(M/F)	Age(years)
Barone Gibbs et al., 2012	America	6 months	3d/w	>45 min	exercise	49	32/17	58.0 ± 5.0
					control	63	37/26	56.0 ± 6.0
Mitranun et al., 2014	Thailand	12 weeks	3d/w	20–30 min	exercise	14	5/9	61.7 ± 2.7
					exercise	14	5/9	61.2 ± 2.8
					control	15	5/10	60.9 ± 2.4
Gholami et al., 2020	Iran	12 weeks	3d/week	30–45 min	exercise	16	NA	53.4 ± 9.1
					control	15	NA	52.2 ± 8.5
Okada et al., 2010	Japan	3 months	3–5d/week	75 min	exercise	21	10/11	61.9 ± 8.6
					control	17	11/6	64.5 ± 5.9
Bouaziz et al., 2019	France	9.5 weeks	2d/week	30 min	exercise	27	7/23	72.9 ± 2.5
					control	29	9/21	74.3 ± 3.4
Azadpour et al. 2017	Turkey	10 weeks	3d/week	25–40 min	exercise	12	female	57.58 ± 4.29
					control	12	female	56.58 ± 4.17
Kwon et al., 2011	Korea	12 weeks	5d/week	60 min	exercise	13	female	55.5 ± 8.6
			3d/week	40 min	exercise	12	female	56.3 ± 6.1
					control	15	female	58.9 ± 5.7
Fecchio et al., 2023	Brazil	10 weeks	3d/week	30 min	exercise	16	male	54 ± 7
					exercise	15	male	55 ± 7
					exercise	15	male	50 ± 11
					control	16	male	52 ± 10
Haynes et al., 2021	Australia	24 weeks	3d/week	50 min	exercise	17	3/14	61.9 ± 5.4
					exercise	18	5/13	62.2 ± 7.4
					control	16	4/12	61.8 ± 7.3
Hildreth et al., 2018	Auraro	12 months	3d/week	NA	exercise	21	male	66 ± 5
					control	19	male	67 ± 5
Mai, 2022	China	8 weeks	3d/week	60 min	exercise	15	female	56.53±1.46
					control	15	female	55.47±1.41
Wu, 2021	China	8 weeks	3d/week	60 min	exercise	16	female	58.12±5.21
					control	16	female	55.12±5.44
Chen et al., 2022	China	12 weeks	5d/weeks	50 min	exercise	15	female	57.60±3.20
					control	15	female	58.33±3.06
Luo, 2021	China	12 weeks	3d/week	40 min	exercise	40	27/13	67.32±9.46
					control	40	24/16	66.54±10.32
Sun, 2019	China	24 weeks	5d/weeks	40–50 min	exercise	15	male	40–50
					control	15	male	40–50
Lu et al., 2012	China	12 weeks	3d/week	60 min	exercise	56	26/30	54.61±7.25
					control	47	20/27	52.36±6.75
Wang, 2019	China	12 weeks	5d/weeks	50 min	exercise	15	female	57.6 ± 3.2
					control	15	female	58.3 ± 3.1
Lv et al., 2019	China	NA	3–5d/weeks	45 min	exercise	70	38/32	63.0 ± 10.1
					control	70	40/30	65.1 ± 12.0
Liu et al., 2007	China	24 weeks	NA	60 min	exercise	17	NA	NA
			NA	NA	exercise	16	NA	NA
					control	17	NA	NA
McDermott et al., 2009	American	24 weeks	3d/week	40 min	exercise	37	NA	NA
			3d/week	NA	exercise	36	NA	NA
					control	28	NA	NA

3.3. *Presence of adverse effects*

A network meta-analysis was not performed for adverse effects since none of the included RCTs reported adverse effects among their participants.

3.4. *Publication bias*

An FMD comparison-corrected funnel plot suggested that there may be some degree of publication bias among the included RCTs (Fig. 5), which may lead to an overestimation of the effect size. Therefore, the meta-analysis results should be interpreted cautiously.

3.5. *Forest plot*

A forest plot was used to visualise the estimated effect sizes and their 95 % CIs for FMD across the various exercise modalities. Each horizontal line represents a comparison, with the centre point indicating the effect size estimate. The length of the horizontal lines represents the CI, and the zero-effect line is shown on the vertical axis. The overall effect size is depicted by a diamond, where the centre indicates the combined effect estimate and the ends represent the 95 % CI of the combined effect. The forest plot showed that, compared to CON, the effect sizes for AE and RE do not cross the zero-effect line, indicating that their overall effects are statistically significant (Fig. 6).

4. Discussion

Middle-aged and older adults are susceptible to endothelial dysfunction due to factors such as ageing, declining physical function and underlying chronic diseases, which increase the risk of cardiovascular diseases. Therefore, investigating methods to improve endothelial function in this demographic is of paramount clinical significance. Our study conducted a network meta-analysis to comprehensively compare

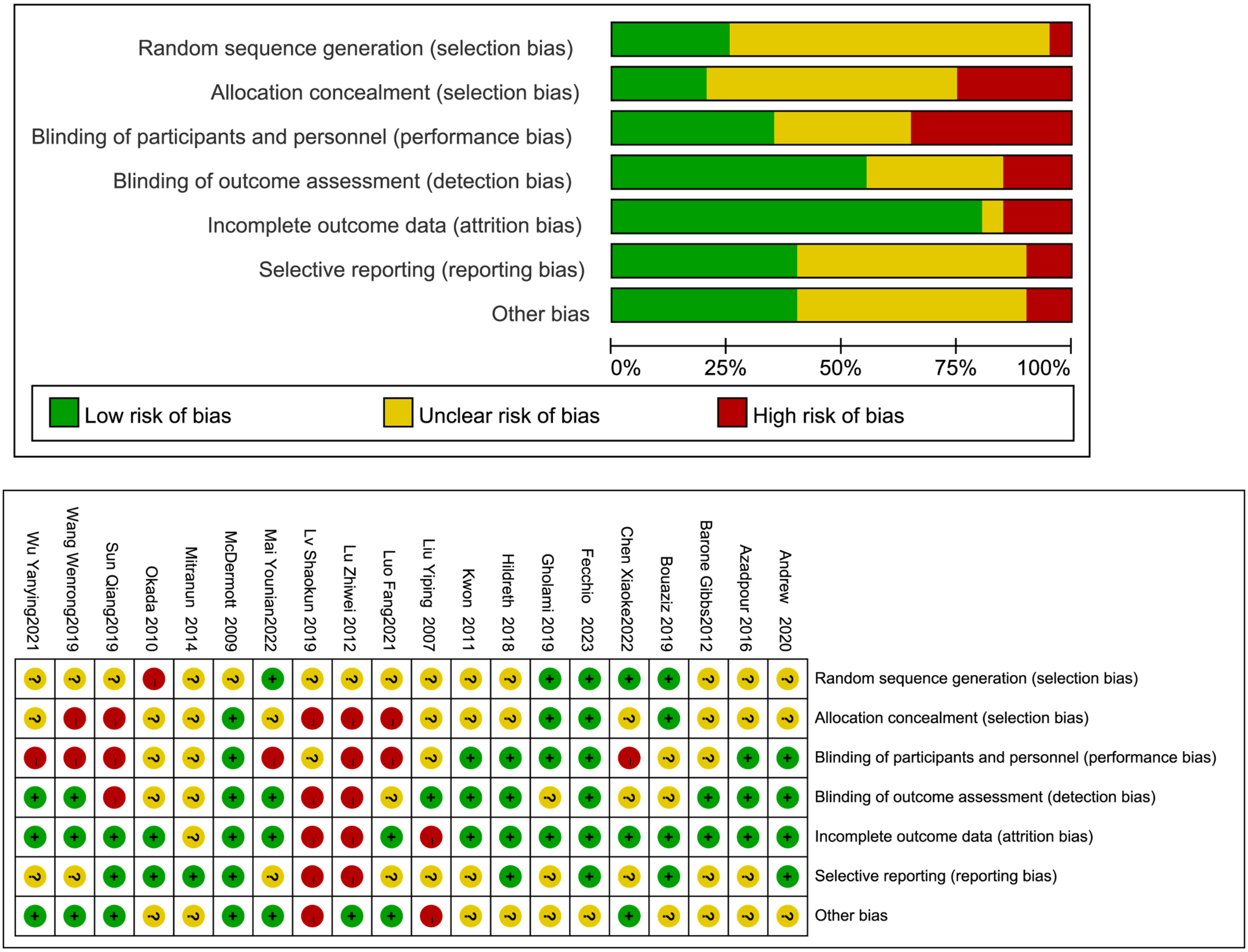

Fig. 2. Quality assessment of the selected RCTs using the Cochrane Risk of Bias tool.
(Upper panel) Risk-of-bias graph: a review of the authors' judgments about each risk of-bias item presented as percentages across all included studies.
(Lower panel) Risk-of-bias summary: a review of the authors' judgments about each risk-of-bias item for each included study.

the effects of various exercise interventions on endothelial function in middle-aged and older adults. Its results indicated that moderate-intensity AE significantly enhanced FMD in middle-aged and older adults compared to RE, CE, and HIIT. This finding is consistent with previous research and further corroborates the cardiovascular benefits of AE.

Our study's finding that moderate-intensity AE significantly impacts FMD in middle-aged and older adults is consistent with Miele and Headley (2017) finding that AE was more effective than RE in improving endothelial function in individuals with type 2 diabetes (2017). Furthermore, meta-analyses on those who are overweight and obese have suggested the beneficial effects of AE on endothelial function (Cortes et al., 2023).

The improvement in FMD with AE is possibly due to the resulting improvements in long-term aerobic capacity, which was a better predictor of FMD changes in individuals with type 2 diabetes than weight or blood glucose control alone (Kwon et al., 2011). The mechanisms by which AE improves FMD are also associated with its ability to increase metabolic rate, blood circulation, vascular endothelial growth factor and endothelial NO synthase levels and the number of endothelial cells (Jo et al., 2020). The high shear stress placed on the vascular wall due to repeated perfusion also plays a role (Pedralli et al., 2020), with exercise-induced shear stress stimulating endothelial cells to produce NO, leading to endothelium-dependent vasodilation (Jo et al., 2020). In summary, the mechanisms underlying AE's beneficial effect on FMD may involve its associated increases in cardiorespiratory fitness, endothelial cell count and vascular shear stress.

Our study also found that RE had beneficial effects on endothelial function in middle-aged and older adults. This finding is consistent with previous studies demonstrating improved endothelial function in individuals with prehypertension and hypertension following RE. In addition, a meta-analysis by Zhang et al. suggested that RE can improve endothelial function in adults (2021). Moreover, an eight-week home-based resistance band training programme for older adults improved age-related microcirculatory endothelial vasodilation (Smith et al., 2017). However, in older adults with type 2 diabetes, a 12-week RE programme did not significantly change endothelial function (Rech et al., 2019). This disparity in outcomes may be related to differences in the frequency of RE used in these studies, as RE at a higher frequency has been suggested to enhance endothelial function (Ashor et al., 2015). Moreover, evidence suggests that low- to moderate-intensity RE may be more effective in improving endothelial function than high-intensity training (Zhang et al., 2021).

The mechanism underlying the improvement in endothelial function observed with RE may involve increased blood flow shear stress as well as reduced oxidative stress and sympathetic nervous system activity.

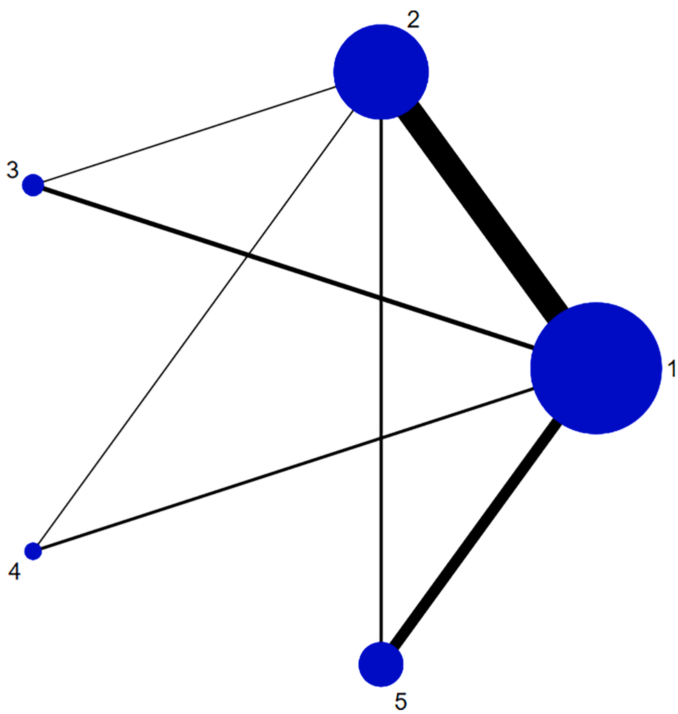

Fig. 3. Network meta-analysis diagrams of eligible comparisons.
Each line's width is proportional to the number of RCTs. Each circle's size is proportional to the number of randomly assigned participants (sample size). Key: 1, CON; 2, AE; 3, CE; 4, HIIT; 5, RE.

Table 3
Network meta-analysis of FMD.

AE				
0.02 (−2.41,2.44)	**HIIT**			
0.20 (−0.94,1.34)	0.19 (−2.35,2.73)	**RE**		–
0.28 (−1.72,2.28)	0.26 (−2.73,3.26)	0.08 (−2.01,2.16)	**CE**	
1.54 (0.75,2.34)	1.53 (−0.83,3.89)	**1.34 (0.37,2.31)**	1.26 (−0.59,3.12)	**CON**

During RE, muscle contractions cause temporary ischaemia due to the mechanical compression of blood vessels. Upon muscle relaxation, the release of blood flow compression leads to congestion and a subsequent increase in shear stress (Tinken et al., 2010). Additionally, the significant increase in blood flow to active muscles to meet the metabolic demands of exercise potentially increases shear rates and elevates NO production or bioavailability, thereby facilitating vasodilation (Di Francescomarino et al., 2009). The increased blood flow and shear stress associated with low- to moderate-intensity RE thus leads to improved endothelial function (Tinken et al., 2009). Furthermore, regular low- to moderate-intensity RE can enhance antioxidant capacity, reduce oxidative stress, promote endothelial adaptation and maintain the balance between sympathetic and parasympathetic nervous system activity (Zhang et al., 2021).

Previous research has shown positive effects of HIIT programmes on endothelial function in middle-aged and older adults. One study on endothelial function in postmenopausal women comparing eight-week HIIT and moderate-intensity continuous training (MICT) interventions found that HIIT effectively improved endothelial function, surpassing MICT (He et al., 2022). Meta-analyses focusing on individuals who are obese and overweight also confirmed that exercise training, particularly HIIT, could enhance endothelial function in these populations (Sabouri et al., 2023). Similarly, HIIT has been demonstrated to effectively improve FMD in those with type 2 diabetes and hypertension and positively affect endothelial function in older adults (O'Brien et al., 2020). HIIT's role in improving FMD may be attributed to its high intensity, as there is a significant positive correlation between AE intensity and endothelial function (Ashor et al., 2015). However, our study did not find HIIT to have a positive effect on endothelial function in middle-aged and older adults, possibly due to the limited number of RCTs included in its analysis.

In addition to AE, RE and HIIT, the potential effects of CE on endothelial function have been explored in recent years. An RCT demonstrated that CE improved endothelial function in individuals with prehypertension and hypertension (Pedralli et al., 2020). However, a study on women with obesity undergoing a CE programme found no improvement in endothelial function after three months of separate AE and CE (Ratajczak et al., 2019). This finding is consistent with the results of our study. However, a meta-analysis on endothelial function in individuals with type 2 diabetes found CE to effectively improve vascular function (Chen et al., 2023). The inconsistency in results may be attributed to differences in the populations included in the studies.

In summary, why is AE most effective in improving endothelial function? Firstly, AE can significantly improve cardiorespiratory function (Boileau et al., 1999), including enhanced cardiac pumping capacity and pulmonary gas exchange capability. These improvements help to increase blood flow velocity and blood shear stress, thereby promoting the release of vascular active substances such as NO by vascular endothelial cells (Uematsu et al., 1995). NO is an important mediator of vasodilation, and its increased release improves FMD.

Secondly, AE can improve endothelial function through various pathways, including reducing oxidative stress (Seals et al., 2019), reducing the inflammatory response (Boeno et al., 2020), and increasing antioxidant enzyme activity (Claudio et al., 2017; E1 Assar et al., 2022). These effects help protect endothelial cells from damage and maintain their normal structure and function, thereby promoting improvement in endothelial function. In addition, long-term AE training can promote the vascular generation and remodelling processes, including improving vascular density (Wu et al., 2018), vascular structure (Song et al., 2022) and vascular elasticity (Lan et al., 2023), contributing to better vascular responsiveness and increased FMD. Moreover, AE promotes the proliferation and differentiation of vascular endothelial progenitor cells, providing new cellular sources for vascular repair and regeneration (Tan et al., 2021). Furthermore, AE enhances lipid and glucose metabolism, lowering lipid and glucose levels and helping to reduce lipid deposition in vessel walls and the formation of advanced glycation end-products, thereby protecting vascular endothelial cells from damage (Kim et al., 2022; Ammar 2015).

Lastly, AE can modulate the neuroendocrine system by reducing sympathetic nervous system activity and increasing parasympathetic nervous system activity (Lin and Lee, 2018). This modulation helps to reduce vascular spasm and constriction, increase vascular dilation, and influence endothelial function. Therefore, AE improves endothelial function through multiple pathways, including enhancing cardiorespiratory fitness, exerting anti-inflammatory and antioxidant effects, promoting vascular generation and remodelling, improving lipid and glucose metabolism, and regulating the neuroendocrine system.

4.1. Strengths and limitations of this review

Our study represents the first network meta-analysis examining the effects of different exercise modalities on endothelial function in middle-aged and older adults. Network analysis enables the comprehensive consideration of multiple exercise modalities' impacts on endothelial function, revealing their potential correlations and interactions. Constructing intricate network relationships can provide a deeper understanding of the relationship between exercise and endothelial function and achieve more profound analytical results. Exercise is also widely

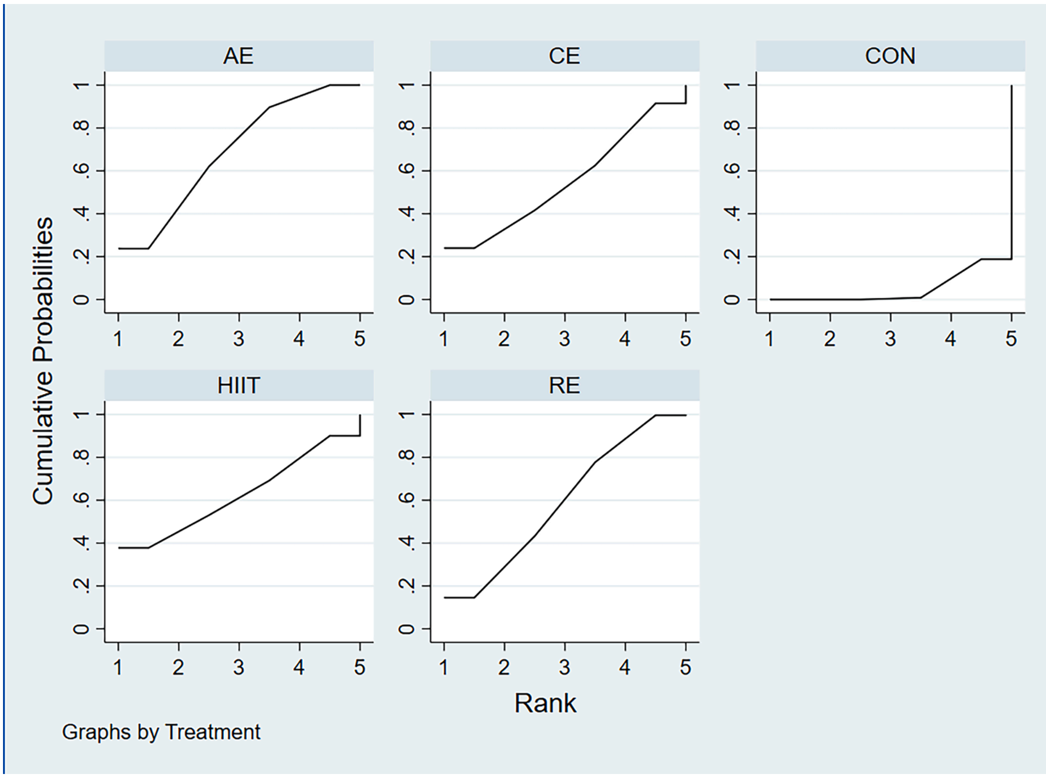

Fig. 4. Cumulative probability ranking curves for the different interventions. The greater the area under the curve, the more effective the intervention.

Table 4
Relative treatment rankings.

Treatment	SUCRA	PrBest	MeanRank
CON	4.9	6.6	4.8
AE	68.9	22.1	2.3
CE	55.5	24.8	2.8
HIIT	62.5	39.0	2.5
RE	58.8	14.1	2.7

recognised as an effective means of improving endothelial function. Through exercise, middle-aged and older adults can enhance vascular elasticity and reduce vascular wall fat deposition, thereby improving blood circulation and reducing the risk of cardiovascular diseases. These established positive physiological effects provide a robust theoretical foundation for network analysis, rendering our study's findings more persuasive.

However, our study had several limitations. Firstly, network meta-analysis requires high-quality and comprehensive data, and any missing or low-quality data may affect the accuracy and reliability of the results. Collecting and processing data for middle-aged and older adults can be challenging due to the presence of chronic diseases and physiological changes, which may cause substantial differences in vascular function and metabolic status among participants and, in turn, affect the accuracy and reliability of the data. Therefore, we opted to use FMD as the primary outcome metric to assess vascular endothelial function. Before data collection, we conducted rigorous screening and evaluation to ensure the reliability and representativeness of the data. Then, we thoroughly reviewed and cleaned the collected data, eliminating duplicates, errors and incomplete entries to ensure our analysis was accurate and reliable.

Secondly, the network meta-analysis included studies that may vary in methodological quality, such as inadequate randomisation and small sample sizes, which may affect the reliability of the results. Therefore, a quality assessment was conducted during the screening process. Additionally, the selected studies may be susceptible to publication bias, as studies with positive results are more likely to be published, whereas those with negative results may be overlooked, potentially biasing the analysis towards supporting a particular intervention. Finally, the number of studies included in our study for each exercise modality, particularly HIIT, was relatively limited. Therefore, future research should expand the number of studies on this topic.

4.2. *Practical significance and perspectives*

Our network meta-analysis results can provide scientific evidence for clinicians to formulate exercise prescriptions tailored to middle-aged and older adults. Depending on specific patient characteristics such as age, health status and exercise habits, recommendations can be made regarding the most suitable types and intensities of exercise to improve endothelial function and prevent cardiovascular diseases. Furthermore, as an advanced statistical method, network meta-analysis not only facilitates the exploration of different exercise modalities' effects on endothelial function but also advances the field of sports medicine. Future studies can apply this method to research in other fields to promote advances in the broader medical field.

Indeed, our study also provides directions for future research. Firstly, while existing studies may have already covered various exercise modalities, future studies can further refine categorisations, such as exercise intensity, duration, frequency and other specific metrics, to more accurately investigate the specific effects of different exercise modalities on endothelial function. Secondly, increasing sample sizes and expanding the scope of studies can enhance the representativeness and reliability of their results. For example, studies targeting middle-aged and older adults from different countries and with different health conditions can further validate the generalisability of existing conclusions. Thirdly, future research could integrate factors such as age, sex, underlying diseases, and lifestyle habits to explore how they collectively mediate the relationship between endothelial function and exercise type. Lastly, building upon the current foundation and delving deeper

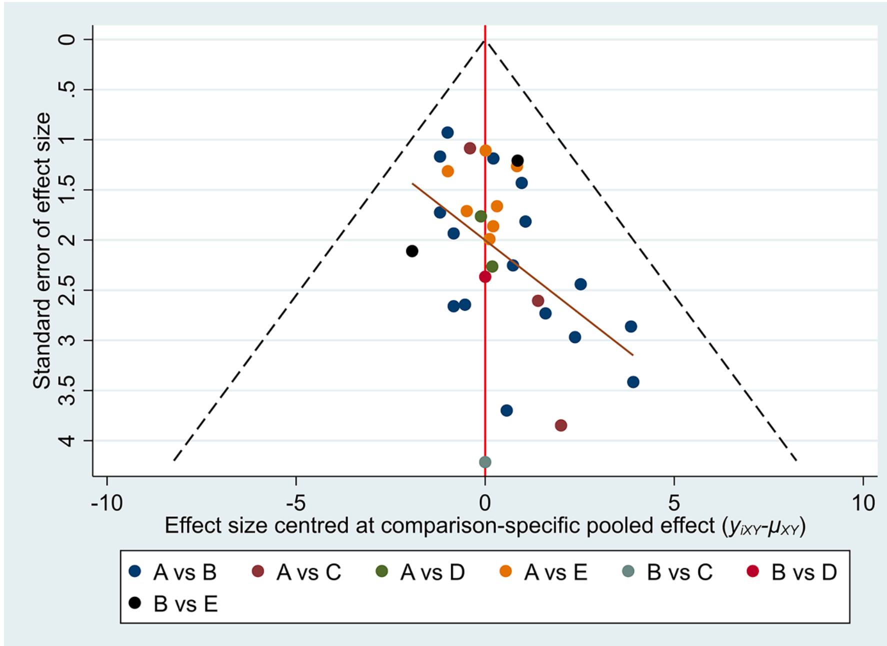

Fig. 5. The FMD comparison-corrected funnel plots.

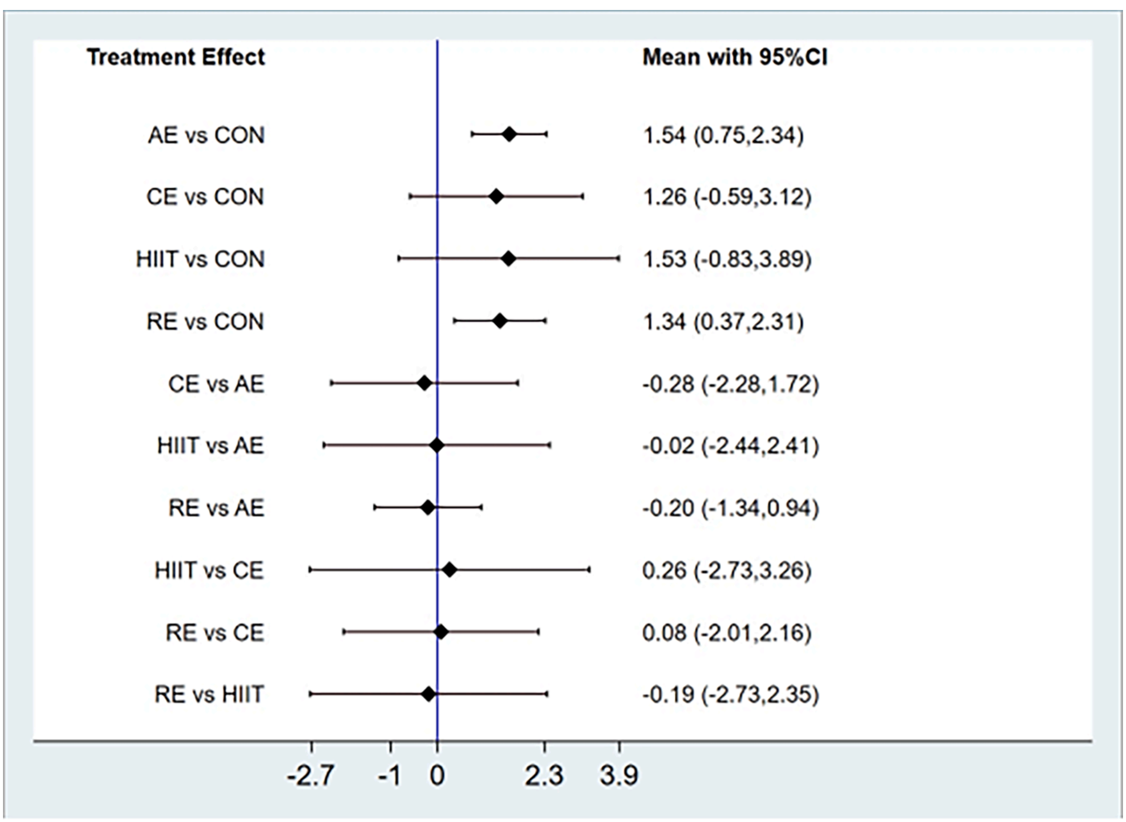

Fig. 6. Forest plot for FMD.

into the physiological mechanisms through which different exercise modalities affect endothelial function, such as the inflammation response, oxidative stress and metabolic pathways, can provide a greater scientific basis for prescribing exercise.

5. Conclusions

This network meta-analysis is the first to examine the effects of different exercise modalities on endothelial function in middle-aged and older adults. It demonstrated that AE is the most effective modality for improving endothelial function in this demographic. RE similarly improved endothelial function in middle-aged and older adults, though further research is needed to elucidate the effects of CE and HIIT. It also provided theoretical support for exercise prescriptions in middle-aged and older adults, enriching the theoretical framework linking exercise with endothelial function.

A statement that all authors have seen and approved the manuscript

All authors have seen and approved the manuscript.

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CRediT authorship contribution statement

Qin Chen: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xin Gao:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chen Wang:** Methodology, Writing – review & editing. **Peizhen Zhang:** Project administration, Resources, Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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